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EPIDEMIOLOGICAL CHARACTERISTICS OF INVASIVE MENINGOCOCCAL DISEASE IN THE SPLIT-DALMATIA COUNTY 1996-2010

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SUMMARY – The aim of this paper is to present epidemiological features of reported patients with invasive meningococcal disease in the Split-Dalmatia County in the period from January 1996 to December 2010. During the 15-year period (1996-2010), a total of 119 patients were reported to have invasive meningococcal disease, yielding a mean annual incidence rate of 1.7/100,000 inhabitants. There were 69 (58%) male and 50 (42%) female patients. Five of 119 patients died, yielding a case fatality rate of 4.2%. Among 83/119 (70%) cases with proven etiology, serogroup was determined in 56/83 (67.5%) patients, whereas in 28/83 (32.5%) patients serogroup could not be determined. The most common serogroup was B, found in 43/56 (76.8%) patients. During the 1996-2010 period, dissemination of the disease in epidemic proportions was not recorded.

Key words: *Meningitis, meningococcal – epidemiology; Croatia; Split-Dalmatia County*

Introduction

Meningococcal disease is a broad term used to describe different clinical syndromes caused by infection with *Neisseria (N.) meningitidis*, and the two main clinical forms of invasive meningococcal disease are meningitis and meningococcemia[1]. Today, it poses a major public health problem in underdeveloped as well as in developing countries. Although invasive meningococcal disease affects a relatively small number of people in developed countries, it is a public health problem there too due to the very severe clinical picture, high mortality, and possible complications. In most countries, *N. meningitidis* (meningococcus) is recognized as the leading cause of meningitis and fulminant septicemia[2]. After the introduction of routine vaccination against *Haemophilus influenzae* type b (Hib)[3] and the growing use of vaccines against *Streptococcus pneumoniae*[4], *N. meningitidis* is becoming the leading cause of bacterial meningitis in children and young adults in the United States and is the second most common cause of community acquired bacterial meningitis in adults[5,6]. According to the polysaccharide capsule antigens, we differentiate 12 meningococcal serogroups, and most forms of the invasive meningococcal disease are caused by meningococci of the A, B, C, X, W135 and Y serogroups[7].

According to the Croatian National Institute of Public Health, Department of Epidemiology, the incidence rate of invasive meningococcal disease in Croatia in the 2000-2010 period ranged from 0.8/100,000 to 1.4/100,000 inhabitants, which puts Croatia among countries with low incidence rates[2,8,9]. In the same period, the case fatality rate (CFR) in certain age groups ranged from 0% to 12.5%[8]. The incidence and CFR are relatively constant, showing no major deviation from previous decades. The disease occurs sporadically, and is usually caused by *N. meningitidis* serogroup B, followed by serogroup C, and rarely serogroup W135[6].

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Patients and Methods

Hospital and primary care physicians are obliged by law to report an occurrence of invasive meningococcal disease by a preformatted registration card to the Department of Epidemiology, Institute of Public Health of the Split-Dalmatia County, as a "meningitis epidemica" entity that includes epidemic meningitis and meningococcal sepsis[10,11]. The invasive meningococcal disease is reported as ICD-10 A39.0-A39.2[12].

In order to obtain more accurate data on those suffering from invasive meningococcal disease, medical histories obtained from Clinical Department of Infectious Diseases, Split University Hospital Center, were inspected. For optimal data processing, the information obtained from medical histories was compared with data from the registration of infectious diseases recorded at Department of Epidemiology, Institute of Public Health of the Split-Dalmatia County. All laboratory analyses were performed at Department of Clinical Microbiology, Split University Hospital Center, and only a small part of them at Department of Acute Respiratory Infections, Dr. Fran Mihaljević University Hospital for Infectious Diseases in Zagreb.

Table 1. Reported cases of invasive meningococcal disease, annual incidence rates per *100,000 inhabitants and case fatality rate in Split-Dalmatia County, 1996-2010*

Year	Reported cases	Annual incidence rate *per* 100 000 inhabitants	Number of death cases	Case fatality rate (%)
1996	9	1.9	0	0
1997	9	1.9	0	0
1998	9	1.9	0	0
1999	16	3.4	0	0
2000	7	1.5	0	0
2001	4	0.9	0	0
2002	7	1.5	0	0
2003	5	1.1	0	0
2004	5	1.1	0	0
2005	13	2.8	1	8
2006	4	0.9	1	25
2007	12	2.6	1	8
2008	3	0.6	1	33
2009	8	1.7	1	13
2010	8	1.7	0	0
Total/Mean	119	1.7	5	4.2

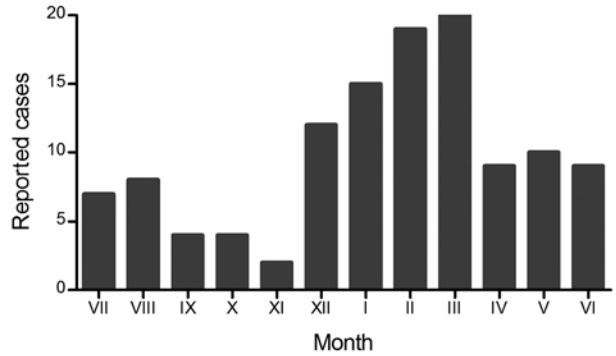

Fig. 1. Seasonal distribution of invasive meningococcal disease cases reported in Split-Dalmatia County, 1996-2010 (N=119).

This retrospective study included cases of invasive meningococcal disease recorded in the period from January 1996 to December 2010. The criteria for diagnosis were clinical signs and laboratory findings. The gold standard for the diagnosis of invasive meningococcal disease is isolation of *N. meningitidis* from normally sterile body fluids, mainly blood or cerebrospinal fluid (CSF)[13]. Those whose diagnosis was based on the clinical signs compatible with meningococcal disease were also considered as invasive meningococcal disease. The analysis was carried out in relation to the incidence rate, age-specific rate by gender calculated on the basis of 100,000 inhabitants in each age group according to the 2001 census[14], CFR, seasonal dynamics, similarity of some clinical forms of the disease, etiologic diagnosis from primarily sterile blood and/or CSF, and the share of isolated pathogens according to serogroups. According to data from that census, the Split-Dalmatia County had 463,676 inhabitants[14].

Results

The number of reported cases, deaths and patients with invasive meningococcal disease in the Split-Dalmatia County according to years of the study period are shown in Table 1. During the 1996-2010 period, 119 patients with invasive meningococcal disease were recorded in the Split-Dalmatia County, yield-

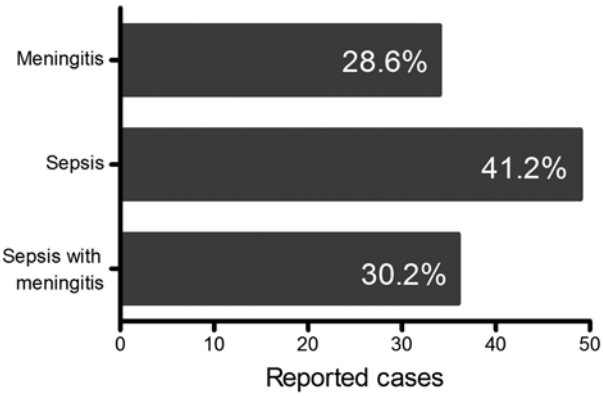

Fig. 2. Clinical presentation of invasive meningococcal disease in Split-Dalmatia County 1996-2010 (N=119).

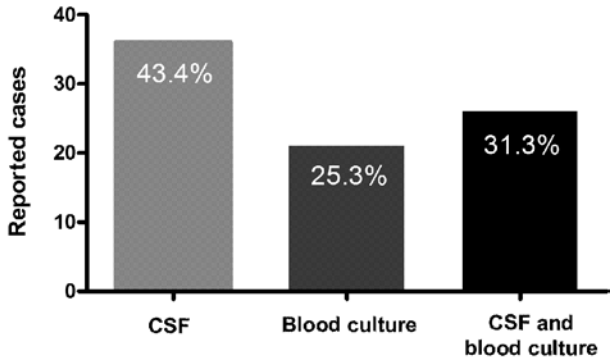

Fig. 3. Etiologic diagnosis of invasive meningococcal disease from blood and/or cerebrospinal fluid (N=83).

ing an annual average of eight patients and a mean annual incidence rate of 1.7/100,000 inhabitants. Five of these 119 (4.2%) patients died. Two of the five deceased patients were under one year of age, two were in the 1-4 age group and one was in the 10-14 age group, accounting for a CFR of 5.4% in this age group.

The cases of patients suffering from invasive meningococcal disease were recorded throughout the year and most cases, i.e. 66 (55.5%), were reported in winter and spring months, while ten (8.4%) cases were reported in autumn months (Fig. 1).

During the study period, there were 69 (58%) male and 50 (42%) female patients. The overall patient median age was 4.2 years (ranging from one month to 81 years). The mean annual male and female incidence rate in the 1996-2010 period was 2.0/100,000 and 1.4/100,000, respectively. The mean male age-specific incidence rate was highest in the age under one year (26.7/100,000) and lowest in the 25-44 and >65 age groups (0.2/100,000). The highest incidence rate for females was in the 1-4 age group (15.6/100,000) and lowest in the 25-44 age group (0.1/100,000) (Table 2).

Invasive meningococcal disease was clinically manifested as meningococcal sepsis in 49/119 (41.2%), followed by meningitis and sepsis in 36/119 (30.2%), and meningitis in 34/119 (28.6%) patients (Fig. 2).

Table 2. Reported cases of invasive meningococcal disease, annual incidence rates by age groups and sex distribution, Split-Dalmatia County, 1996-2010

Age group (yrs)	Reported cases			Incidence rate *per* 100,000 inhabitants		
	Total/%	Male	Females	Total	Male	Female
<1	16 (13.4)	11	5	19.7	26.7	12.5
1-4	46 (38.7)	21	25	14.2	12.8	15.6
5-9	13 (11.0)	8	5	3.0	3.6	2.4
10-14	18 (15.1)	9	9	3.9	3.9	4.1
15-19	15 (12.6)	12	3	3.0	4.8	1.3
20-24	7 (5.9)	5	2	1.4	2.0	0.8
25-44	3 (2.5)	2	1	0.2	0.2	0.1
45-64	(0.0)	0	0	0.0	0.0	0.0
≥65	1 (0.8)	1	0	0.1	0.2	0.0
Total	119	69 (58%)	50 (42%)			

Table 3. Neisseria meningitidis *serogroups identified in invasive meningococcal disease in Split-Dalmatia County, 1996-2010*

Year	Reported cases	Isolation from blood and/or CSF	Serogroups			
			NM*	NMB	NMC	NW135
1996	9	4	2	2	0	0
1997	9	6	1	4	1	0
1998	9	6	5	0	1	0
1999	16	14	14	0	0	0
2000	7	6	3	3	0	0
2001	4	2	0	2	0	0
2002	7	4	0	2	2	0
2003	5	2	0	2	0	0
2004	5	3	0	2	1	0
2005	13	10	2	4	2	2
2006	4	2	0	2	0	0
2007	12	8	0	7	1	0
2008	3	3	0	3	0	0
2009	8	7	0	5	0	2
2010	8	6	0	5	1	0
Total	119	83	27	43	9	4

*Serogroup was not determined; CSF = cerebrospinal fluid.

The etiologic diagnosis was confirmed in 83 (70%) patients, as follows: by CSF culture in 36 (43.4%), by blood culture in 21 (25.3%), and by both CSF and blood culture in 26 (31.3%) patients (Fig. 3).

Serogroup was determined in 56 of 83 (67.5%) cases with confirmed etiology. Serogroup B was most common, found in 43 (76.8%) patients, followed by serogroup C in nine (16%) and serogroup W135 in four (7.2%) patients (Table 3).

Discussion

In the Split-Dalmatia County, the invasive meningococcal disease incidence rates in the 1996-2010 period ranged from maximum 3.4/100,000 inhabitants in 1999 to minimum 0.6/100,000 inhabitants in 2008, showing significant fluctuations during the 15-year study period. The mean annual rate for the entire period was 1.7/100,000. In Croatia, the incidence of invasive meningococcal disease during the 2000-2010 period ranged from 0.8 to 1.4/100,000 inhabitants, and in the 1996-2010 period the mean annual growth rate in Croatia was 1.1/100,000, which was similar to the incidence rate in the Split-Dalmatia County for the same period[8,15]. The total annual incidence rate in Europe between 1999 and 2006 was 1.09/100,000 inhabitants[16], while in the same period the mean incidence rate in the Split-Dalmatia County was 1.6/100,000, which is nearly twice the mean rate recorded in Europe. In 2009, the incidence rate of invasive meningococcal disease in Europe was 0.89/100,000 and had a tendency to stabilize from 2006, with a significant decline compared with the rate in 1999 (1.9/100,000). This is explained by the fact that vaccination against diseases caused by meningococcus group C started from 1999[17]. In the Split-Dalmatia County, however, there was no indication of decreasing incidence in the study period. The manufacture of vaccine for meningococcus serogroup B has recently been approved by the European Commission[18].

Most patients in the Split-Dalmatia County were recorded in the 1-4 age group (38.7%), followed by the 10-14 year-group (15.1%) and under one year of age (13.4%), with a concurrent decrease in its incidence with the increase in age. In the 2003-2010 period, 195 patients were treated for invasive meningococcal disease at Dr. Fran Mihaljević University Hospital for Infectious Diseases in Zagreb, 71.3% of them aged 0-14[19], which was very similar to the results obtained for the Split-Dalmatia County for the same age group (78.2%). According to data for Europe in 2006, the age distribution of patients was similar to that recorded in the Split-Dalmatia County, but with a significantly lower proportion of patients aged 0-14 compared to the Split-Dalmatia County (34.9%)[16].

The analysis of age-specific incidence rates in the Split-Dalmatia County indicated the highest rate in the <1-year age group (19.7/100,000), followed by 14.2/100,000 in the 1-4 age group, while in other age groups it ranged from 3.9/100,000 to 0.1/100,000. The highest incidence rate of invasive meningococcal disease in the <1-year age group was recorded in Belgium in 2006 (17.93/100,000), followed by 6.51/100,000 in the 1-4 age group, while in other age groups it ranged from 3.9/100,000 to 0.17/100,000[16]. According to 2009 data in Europe, children younger than five had the highest rate of confirmed cases of invasive meningococcal disease (7.37/100,000), followed by 15-24 (1.44/100,000) age group, whereas in older age groups the disease was extremely rare[17].

In the Split-Dalmatia County, out of 119 patients with invasive meningococcal disease recorded in the study period, there were 69 (58%) male and 50 (42%) female patients. A similar ratio was also recorded at Dr. Fran Mihaljević University Hospital for Infectious Diseases in Zagreb[20]. In Europe, the male to female ratio was 1.12:1.0[17]. In the Split-Dalmatia County, the analysis of age-specific incidence rates by gender showed the rates in all age groups to be higher in male, except for the 1-4 age group, while the highest difference in incidence rates for both genders was found in the <1-year age group, where the male rate was two-fold higher compared to female (26.7:12.5/100,000).

According to data for 2009, in Europe there was a rate of 0.97/100,000 for male and 0.82/100,000 for female patients[17]. In comparison, the mean annual rate in the Split-Dalmatia County was double for male (2.0/100,000) and higher for female (1.4/100,000) patients.

Patients suffering from invasive meningococcal disease were recorded throughout the year, with the majority occurring in winter and spring months (55.5%), correlating with the increased incidence of respiratory viral infections. The lowest number of cases were recorded in September, October and November (8.4%). The same seasonal distribution was observed by other authors[5,6,17,19-21]. In the Split-Dalmatia County, despite the use of modern diagnostics and treatment, five (4.2%) patients died from invasive meningococcal disease during the study period. The same CFR (4.1%) was recorded at Dr. Fran Mihaljević University Hospital for Infectious Diseases in Zagreb in the 2003-2010 period[19]. Four of the five deceased patients in the Split-Dalmatia County were aged 0-4 years (4/62; 6.5%), which is the age with the highest reported CFR. In the 0-14 age group there were 5.8% of deaths (5/93), while at Dr. Fran Mihaljević University Hospital for Infectious Diseases this ratio was slightly lower and amounted to 3.7%[20]. In the Split-Dalmatia County, there were no deaths recorded among adults and older population. In some European countries in 2009, the CFR ranged from 5% to 10%[17]. Invasive meningococcal disease in the Split-Dalmatia County was clinically most commonly manifested as meningococcal sepsis (49/119; 41.2%). At Dr. Fran Mihaljević University Hospital for Infectious Diseases in Zagreb, meningococcal sepsis with meningitis was recorded as the most common clinical form in the 2003-2010 period (106/54.3%)[19], while in some European countries meningococcal meningitis was the most common disease manifestation[21].

Cerebrospinal fluid and blood are the most common and most convenient patient samples with positive cultures. In the Split-Dalmatia County, the etiology of the disease was confirmed in 83 (70%) patients from primarily sterile blood and/or CSF. Blood culture was positive in 21 (25.3%) patients, while both positive blood and CSF cultures were recorded in 26 (31.3%) patients.

At Dr. Fran Mihaljević University Hospital for Infectious Diseases, the etiologic diagnosis from primarily sterile materials was positive in 80% of patients, while the causative agent was detected by cultivation in approximately 37% of patients[19]. A low percentage of

N. meningitidis isolated from blood and/or CSF culture was only partially an effect of prior therapy (a chance for the blood culture to be positive after received antibiotic therapy is often less than 5%, and in patients who have not previously received antibiotics, the percentage of positive blood culture can rarely reach 50%)[22]. In 56 patients from the Split-Dalmatia County with *N. meningitidis* as the causative agent and identified serogroup, the most commonly identified serogroup was B in 43 (76.8%) patients, followed by serogroup C in nine (16.1%) and serogroup W135 in four (7.1%) patients. In 28 patients, serogroup was not determined because there was no serum available. In Croatia, the disease is also commonly caused *by N. meningitidis* serogroup B, followed by serogroup C and rarely serogroup W135[6,19,20]. In Europe, the majority of cases are caused by serogroup B, particularly in countries that have introduced serogroup C meningococcal conjugate vaccines[21,23,24].

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Sažetak

EPIDEMIOLOŠKE ZNAČAJKE INVAZIVNE MENINGOKOKNE BOLESTI NA PODRUČJU SPLITSKO-DALMATINSKE ŽUPANIJE U RAZDOBLJU OD 1996. DO 2010. GODINE

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Cilj rada je prikazati epidemiološke značajke invazivne meningokokne bolesti na području Splitsko-dalmatinske županije na osnovi prikupljenih prijava ove bolesti u razdoblju od siječnja 1996. do prosinca 2010. godine. U promatranom razdoblju ukupno je prijavljeno 119 bolesnika od invazivne meningokokne bolesti, što čini prosječnu godišnju stopu incidencije od 1,7/100.000 stanovnika. Od prijavljenih bilo je 69 (58%) muških i 50 (42%) ženskih bolesnika. Umrlo je 5/119 bolesnika, što čini stopu smrtnosti od 4,2%. Kod 83/119 (70%) bolesnika s dokazanom etiologijom serogrupa uzročnika je određena kod njih 56/83 (67,5%), dok kod 28/83 (32,5%) bolesnika serogrupa nije određena. Najčešća je bila serogrupa B (43/56; 76,8%). U razdoblju od 1996. do 2010. godine nije na ovom području bilo zabilježeno širenje invazivne meningokokne bolesti u epidemijskim razmjerima.

Ključne riječi: *Meningitis, meningokokni – epidemiologija; Hrvatska; Splitsko-dalmatinska županija*